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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,578	09/10/2003	Zsuzanna Nagy	43962-010810	4669

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,578	NAGY, ZSUZANNA	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *19-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6,11 and 12* is/are rejected.

7)☒ Claim(s) *7-10 and 13-18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-18, in the reply filed on 5/23/05 is acknowledged.

2. Claims 19-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/23/05.

3. Claims 1-18 are presently under examination.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 12/3/01. It is noted, however, that applicant has not filed a certified copy of the 0106051 .6 application as required by 35 U.S.C. 119(b).

Drawings

5. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the text in each of the drawings is small and dark and it does not appear that the figures would reproduce well for publication. Additionally, clearer images in Figure 6 are preferred. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. The disclosure is objected to because of the following informalities: To establish the continuity history of the instant application, the first line of the specification should read: --This is a National Stage Application of International Application PCT/GB02/01137, filed 12/3/01.-- As a single inventor has applied for the instant application, statements in the specification such as on page 2, line 30: "Studies by the present inventors" (emphasis added) are in error. The heading --Brief Description of the Drawings-- should appear above line 14 on page 21. The description of Figure 1 on page 21 contains reference to "G1" on line 18. As there is no "G1" present in Figure 1, it would appear that --M1-- was intended. On page 23, line 27, Ficoll is misspelled. The paragraph starting on line 19 of page 26 appears to make improper reference to the figures, i.e. the wrong figure is cited for the data that is presented.

Appropriate correction is required.

Claim Objections

8. The entire claim set is objected to because the claims do not appear in the form of a single sentence. To recite --I claim-- at the head of the claim set would be remedial.

9. Claim1 is further objected to because of the following informalities: the claim does not end in a period. Appropriate correction is required.

10. Claims 7-10 and 13-18 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-6 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. The claims are drawn to a method of screening patients for Alzheimer's disease (AD) where the presence of G1/S checkpoint defect in non-neuronal cells is taken to mean the patient has AD. The specification does not supply sufficient support to convince the skilled artisan that at the time of filing, the inventor had truly determined that the defect observed, was a defect in the G1/S checkpoint.

14. The specification deals with this issue predominantly in Figures 1-5, and pages 26-30. The specification argues that one is assured that the cell cycle defect observed is due to a G1/S checkpoint defect. The basis of the argument is essentially that the AD-related lymphocytes differentially respond to rapamycin and H_2O_2 treatment, two treatments that manifest their

effects in G1, but do not respond differently to doxorubicin treatment, a treatment that affects G2. The problem with this analysis is that the data does not seem to reflect these analyses.

15. All of Figures 2-5 have two panels. The panels on the left are reported to be absolute values while the right panels are reported to be age corrected values. In the context of these studies it is only the age corrected values that should be considered. There are numerous example in the art cited in the specification that bear this out. For example, Araga (Jpn. J. Med. 29:572-575 (1990), of record) found that although there were differences between AD cells and non-AD cells when comparing non-age controlled populations, when comparing AD cells to normal age-matched cells, there was no discernable difference. Additionally, Fischman (Biol. Psychiatry 19:319-327, of record) states: "Observations of cell cycles from five cultures of normal adults (average age 39.6 years), made during the course of other studies in our laboratory, demonstrated an average cell cycle of 21.76 hr. The cell cycles of both the AD patients and their aged controls were 50% higher than these. This may indicate a retardation of the cell cycle in aging, and bears further scrutiny" (page 325, last full paragraph). Clearly then, as is the case with all studies of this kind, it is an improperly controlled study that does not control for all parameters that can be controlled, in the instant case: age. If one compares the right panel of Figure 3, reported to have statistically significant differences, with the right panel of Figure 4, reported to have no statistically significant differences, it would seem impossible to come to the conclusion that the defect is definitively at the G1/S checkpoint. The differences seen in Figure 4 seem to be at least as great as those seen in Figure 3, suggesting that there is indeed a difference in the cell cycle of lymphocytes from different patient groups when treated with doxorubicin. Aside from this, no

mention is made in the specification of the large responses seen in both of these figures for the DNOS cells.

16. This analysis of the data brings forth two problems. First, the basis of concluding that the cell cycle defect is due to a G1/S checkpoint defect is largely based on the alleged differences between the responses of cells from different patient groups when comparing rapamycin and H_2O_2 to doxorubicin. With this data called into question there would seem to be no real support for the claim that the defect is definitively due to a problem in the G1/S checkpoint. Second, the specification ignores the fact that the DNOS cells appear to have the greatest differences relative to the control cells in Figures 3-5. Based on the direction of the claims, this would lead the skilled artisan to conclude that these cells were derived from an AD patient when clearly they are not. This then would lead to a high level of false positives, ultimately resulting in improper treatment for the patients in need.

17. Therefore, the skilled artisan would have no real reason to conclude that the inventor was in possession of the invention of being able to diagnose AD patients based strictly on a defect in the G1/S checkpoint of lymphocytes in these patients. The lack of clear data suggesting that the defect is in the G1/S checkpoint shows an absence of possession, and the lack of data suggesting that the defect observed was specific to lymphocytes from an AD patient also calls in to question one's ability to diagnose AD based strictly on cell cycle defects.

18. Claims 1-6 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying human subject who are likely to have AD by screening for a cell cycle defect in lymphocytes, does not reasonably provide enablement for

diagnosis of AD in those human subject using any non-neuronal cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

19. The claims are drawn to a method of diagnosing AD by screening non-neuronal cells for a defect in the G1/S checkpoint, where a defect indicates that the patient has AD. The further claims address the methods by which the screening would occur. The specification has not convincingly established that the cell cycle defect is due to a G1/S checkpoint defect, has not provided any evidence that the findings regarding lymphocyte proliferation would be applicable to other non-neuronal cell types, and has not provided sufficient evidence that the defects observed would necessarily correlate with true AD. Therefore to practice the full scope of the claims, the skilled artisan would be required to perform undue levels of experimentation.

20. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

21. What does it mean to diagnose a disease? Essentially, it means to determine a disease state that is causing a patient's symptoms. So we must then ask ourselves: does the specification provide sufficient information to allow the skilled artisan to screen lymphocytes for a cell cycle defect and definitively inform a patient that they have or will soon develop Alzheimer's disease?

The data provided in the specification certainly seems to suggest this, however, no true correlation has been shown, because it is well known in the art, and admitted by the applicant in the specification: "A definite diagnosis of Alzheimer's disease can only be made after post mortem examination" (page 5, lines 4-6). Thus, absent a showing that all of those who show the cell cycle defect are later found post-mortem to have the histological hallmarks of AD, one could not be assured that the suspected AD patient was indeed an AD patient.

22. The other question that arises is this: is the detection of a cell cycle defect necessarily indicative of AD? In short, and in concurrence with the above analysis: no. The inventor's motivation for pursuing the possibility that lymphocytes might have a cell cycle defect can be found on pages 2 and 3 of the specification. It is the finding that the development of AD may be due to the inappropriate reentry of neurons into the cell cycle. Much evidence is cited that suggests that cell cycle defects are found in peripheral tissues as well. If it were indeed the case that AD patients have symptoms that are reflected in somatic cells, it certainly would be plausible that other neurological disorders would also show characteristics in non-neuronal cells. Nagy-a (Neuroscience 87:731-739 (1998), of record) teaches that other neurological disorders exist that show similar neuronal cell cycle defects to AD. "Although cell cycle protein expression distinguished AD patients from control subjects it is not specific for AD. We detected cyclin expression in the CA2, CA4 and dentate gyrus in some patients with Pick's disease and in the dentate gyrus of old epileptic patients. Another patient group that expressed large numbers of neurons positive for cyclin B were patients suffering from intractable temporal lobe epilepsy (TLE)" (page 735, first column, last paragraph-second column first paragraph). As this passage clearly indicates, improper cell cycle entry is in no way restricted to AD but can also be found in

other neurological disorders. This does not even consider the obvious disease that is largely due to the misregulation of the cell cycle: cancer. It is certainly plausible that non-neuronal cells from any patients afflicted with Pick's disease, epilepsy, or TLE.

23. Additionally, as discussed above, the data presented in the specification even suggests that the cell cycle defects are not restricted only to lymphocytes derived from AD patients. The specification does not address this, but clearly from Figures 3-5, the DNOS patients have the biggest differences relative to the control group of any of the other groups.

24. This analysis and that presented above in paragraphs 14-16 brings forth two problems as discussed above. First, the basis of concluding that the cell cycle defect is due to a G1/S checkpoint defect is largely based on the alleged differences between the responses of cells from different patient groups when comparing rapamycin and H_2O_2 to doxorubicin. With this data called into question there would seem to be no real support for the claim that the defect is definitively due to a problem in the G1/S checkpoint. Second, the specification ignores the fact that the DNOS cells appear to have the greatest differences relative to the control cells in Figures 3-5. Based on the direction of the claims, this would lead the skilled artisan to conclude that these cells were derived from an AD patient when clearly they are not. This then would lead to a high level of false positives, ultimately resulting in improper treatment for the patients in need.

25. All studies reported in the specification use lymphocytes from patients of different disease states. Thus all effects reported apply to lymphocytes from these patients. The claims are drawn to any non-neuronal cell. The only other non-neuronal cell type addressed in the specification is a brief mention of fibroblasts. There is no evidence provided however that suggests that fibroblast from the patients would have the same responses to the treatments

performed on the lymphocytes. There is guidance presented to even establish how the studies in fibroblasts, or for that matter, any other non-lymphoid, non-neuronal cell. The applicant seems to be relying on previous studies suggesting cell cycle defects in fibroblasts from AD patients, yet no references are cited to support this claim when the claim is made. There is reference to a fibroblast study by Tatebayashi et al. (Dementia 6:9-16 (1995), of record). The problem with relying on this study is that Tatebayashi does not report similar findings to those of the instant application. Tatebayashi detects differences in Ca^{2+} transients specifically in S phase in fibroblast lines of two out of four AD patients studied. The studies in the instant application would suggest that Tatebayashi would see shortening of the cell cycle. Tatebayashi reports no differences of this nature. Thus, the report by Tatebayashi would not convince the skilled artisan that the differences seen in lymphocytes would necessarily be the same type as differences seen in fibroblasts or other non-neuronal cell types.

26. As the idea that AD is a cell cycle related disease is a new one there is still a high degree of unpredictability inherent in any studies pertaining to AD. Thus it would be near impossible for the skilled artisan to extrapolate the results found in lymphocytes to other cell types. In order to extend studies of this nature to non-lymphoid cells, the skilled artisan would be required to engage in an undue level of experimentation.

27. When making an enablement rejection, one first looks to the specification for guidance. AS detailed above, the specification shows cell cycle defects in lymphocytes of patients believed to be suffering from AD and those believed to be in the early stages of AD. Additionally, though, the specification seems to teach that other dementias, defined in the specification as DNOS, also have similar cell cycle defects. Also, though the specification reports to find that the cell cycle

defect is at the G1/S, it does not seem that the data supports this finding, as discussed above. One then looks to the prior art to determine if that which was not specifically disclosed can provide the necessary support. As described, the prior art does not contain any apparent teaching that the cell cycle defect was due to a G1/S checkpoint defect. Additionally, the art fails to support the notion that other non-neuronal cells than lymphocytes, in particular fibroblasts, would have a similar cell cycle defect to that seen by the inventor in lymphocytes. It is thus apparent that the skilled artisan would be unable to practice the full scope of the claimed invention without engaging in an undue level of non-trivial experimentation.

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

29. Claims 1-6 and 11-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Nagy-b (Neurosci. Lett. 317:81-84 (2002), newly cited). It is clear that Nagy-b is a paper reporting the same data presented in the specification of the instant application, as the figures of the paper are the same as the Drawing in the application. As such Nagy-b necessarily anticipates the instant application. Absent any evidence to the contrary, all limitations of the claims are taught by Nagy-b. Perfection of the foreign priority claim will obviate this rejection, assuming sufficient support is present in the foreign application to which priority is claimed.

Conclusion

30. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Stieler (Neuroreport 12:3969-3972 (2001), newly cited) teaches that lymphocytes from AD patients aberrantly responded to various stimuli, showing a deficiency in cell cycle progression. Urcelay (Neurobiol. Dis. 8:289-298 (2001), newly cited) teaches that lymphoblastoid cell lines (LCLs) derived from AD patients more readily proliferate than LCL derived from age matched control patients.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

JAMES KETTER
PRIMARY EXAMINER